

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: 019810/S057**

**APPROVAL LETTER**

NDA 19-810/S-057

Astra Pharmaceuticals, L.P.  
Attention: Gary P. Horowitz, Ph.D.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

FEB - 3 1999

Dear Dr. Horowitz:

Please refer to your supplemental new drug application dated July 31, 1998, received August 3, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your submission dated October 19, 1998 containing revised final printed labeling (no. 7910930) which corrects errors discovered in the final printed labeling (no. 7901928) submitted in this supplement on July 31, 1998.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for revision of the ADVERSE REACTIONS section of the package insert to add the phrases "allergic reactions, including, rarely, anaphylaxis (see also *Skin* below)" and "purpura and/or petechiae (some with rechallenge)." Your submission stated November 1, 1998 as the implementation date for the changes.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted October 19, 1998, no. 7910930). Accordingly, the supplemental application is approved effective on the date of this letter.


If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

 2-3-99

Lilia Talarico, M.D.

Director

Division of Gastrointestinal and Coagulation Drug  
Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

cc:

Archival NDA 19-810/S-057

HFD-180/Div. Files

HFD-180/M. Walsh

HF-2/MedWatch (with labeling)

HFD-002/ORM (with labeling)

HFD-103/ADRA (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-95/DDMS (with labeling)

HFD-820/DNDC Division Director

DISTRICT OFFICE

final: M. Walsh 2/3/99

filename: 19810S57902.ap.doc

APPROVAL (AP)

APPEARS THIS WAY  
ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 019810/S057**

**MEDICAL REVIEW(S)**

DF

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 19-810  
SLR 057 FEB - 2 1999

Sponsor: Astra Merck  
Wayne, PA

Date Submitted: July 31, 1998

DRUG: PRILOSEC® Delayed-Release Capsules (Omeprazole)

Pharmacological Category: Antisecretory, Antiulcer, Proton pump inhibitor

Material Submitted: A supplemental application providing for labeling changes, in accordance with 21CFR 314.70(c) of FDCA

Material Reviewed: As above. In addition:  
a) Additional information on Pt. ☐ No. 19970800129/1998 0300034  
b) Initial examination of the safety database for similar cases

Reviewer: Hugo E. Gallo-Torres, M.D., Ph.D.

**I. BACKGROUND/INTRODUCTION**

In this submission, dated July 31, 1998, the sponsor makes reference to two Agency letters dated March 31, 1998 and June 26, 1998. In these letters the Division recommended that the sponsor consider adding AEs to the labeling for PRILOSEC® as follows:

1. Purpura and petichiae and reduced hearing

In addition, at a meeting on April 29, 1998 with representatives from Astra Merck, P&G and the Divisions of OTC Drug Products and HFD-180, regarding the OTC program with omeprazole, an additional AE (allergic type reactions) was discussed.

## **II. PROPOSED REVISIONS BY THE SPONSOR**

With this supplement, the sponsor is revising the package insert for PRILOSEC® under ADVERSE REACTIONS as follows:

1. *Body as a Whole*: Add the phrase "Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below)"
2. *Skin*: Add the phrase "purpura and/or petichiae (some with rechallenge)"

Supportive documentation was attached which provided a summary of the AEs review in support of these revisions.

### **Comment**

This reviewer agrees with the sponsor's proposal.

The sponsor also has reviewed the supporting information for case MRNo. 1997-0800129/19980300034. This report describes a single patient who experienced partial deafness in June 1997, and reduction in hearing in December 1997 while being treated with OME. A summary of all available information on this patient follows.

#### **Manufacturer's report no. 19970800129**

The patient, a 43 year old man, was prescribed omeprazole 29 mg daily in combination with amoxicillin and clarithromycin on June 7, 1997 for eradication of H pylori. On the same day as this treatment regimen was initiated, he experienced partial deafness accompanied by dizziness, tinnitus, and hypertension. Medical therapy was continued until June 10, 1997 when it was stopped. Deafness persisted until it was reported it had improved in a follow-up report received on November 19, 1997. The patient's medical history was remarkable for a history of kidney transplantation and concomitant medication use, including cyclosporin, simvastatin, and flunisolide. The reporter did not attribute the deafness to omeprazole, but suspected interaction between clarithromycin and cyclosporin.

#### **Manufacturer's report no. 19980300034**

The patient was again prescribed omeprazole 20 mg daily on December 24, 1997, but in combination with amoxicillin and metonidazole for eradication of H pylori. After 5 days of therapy, on December 29, 1997, he experienced what was reported as a reduction in hearing 10% below normal levels and dizziness and hypertension. Additional past medical history was reported of chronic otitis media with repeated interventions, and impaired hearing corrected with the use of a hearing device until the June 7, 1997 partial deafness reported above for 19970800129. The patient continued on cyclosporin for his renal transplantation. Omeprazole and antibiotics were stopped on December 29, 1997, and the diminution of hearing was continuing as of the time of the report. Additional information is being sought.

**NOTE:** The reviewer agrees with the sponsor that this is not a "good case". There is some insinuation of positive rechallenge, but, in reality, additional information is needed.

In addition the sponsor submitted results of a review of the Astra Pharmaceuticals post-marketing safety database for omeprazole. This search produced 37 additional cases of reduced hearing or deafness. These cases can be grouped by the following features:

Feature	N	Causality Assessment <sup>a</sup>			
		NR	U	Poss	Prob
Possible drug-induced hearing deficit	11	6	1	1	3
Unilateral hearing loss	10	5	1	2	2
Other causes <sup>b</sup>	17	5	10	2	0
Total	38	16	12	5	5
a) NR=not related; U=unlikely to be related; Poss=possibly related; Prob=probably related					
b) Other causes refers to sickness, known structural problems, otitis media, past history of intermittent problems.					

According to the sponsor, the majority of cases (27/38 or 71%) have reasonable explanations for the hearing deficit other than a drug-induced event. None of the cases report a positive rechallenge or dechallenge. Of the 11 cases characterized as possibly drug-induced hearing deficits only 4 were judged to be possibly or probably related to omeprazole. The sponsor concludes that at this time, they do not feel that the evidence of association with omeprazole use is clear enough to warrant inclusion in the prescribing information.

### III. REVIEWER'S ASSESSMENT OF DATA

The MO reviewed the case summary reports for each of the cases submitted by the sponsor. These are identified below.

19870700193	19940601337 <sup>1</sup>	19950800060 <sup>6</sup>	19960400109
19881000513	19940800013	19950800100 <sup>7</sup>	19960600003
19900300543	19940800063	19950900113	19960600040 <sup>9</sup>
19901200181	19941200051	19950900130	19960900139 <sup>10</sup>
19901200276	19941200137	19950900131	19970200092
19930501430	19950100064 <sup>2</sup>	19950900132	19970300102 <sup>11</sup>
19930900994	19950400020 <sup>3</sup>	19951000251	19970800129 <sup>a</sup>
19931001289	19950400123 <sup>4</sup>	19951000254	19980300034 <sup>a</sup>
19931201481	19950600042 <sup>5</sup>	19951000296 <sup>8</sup>	19980400097
19940500777	19950600153	19960300075	

a) Same patient

Review of this evidence reveals that, indeed, most cases are confounded, many have reasonable explanations for the hearing deficit other than drug-induced event, except as noted above [possibly case 19970800129/19980300034], none of the cases reported a positive rechallenge. Nonetheless, the cases listed below were assessed either as possibly or probably related to omeprazole or there was a temporal relationship with the discontinuation of the drug and the apparent improvement or disappearing of the side effect. In addition, there were several cases that appear to report a positive dechallenge. Of course, in many instances, more information is needed to allow for firm conclusions to be drawn.

CASE IDENTIFICATION	REMARKS
<p>1. <u>No. 19940601337</u> M patient was placed on Tx with OME (dosage and duration not reported) and developed almost complete deafness of the R ear. Tympanoplasty and meatoplasty were not successful. Had not recovered by June 1994.</p>	<p>Firm to provide additional information requested.</p>
<p>2. <u>No. 199501000064</u> M63 given OME 40 mg for DU. Experienced hearing loss and was hospitalized on the day following D/C of the drug. (Recovered following rheological therapy.)</p>	<p>The reporter indicated that the event was probably/ possibly related to OME (Antra) therapy. (Closed)</p>
<p>3. <u>No. 19950400020</u> M56, developed L hearing impairment, ca. 6 months after starting OME 20 to 40 mg/day for Tx of RE.</p>	<p>The reporter indicated OME (Antra) was most probably related to the events.</p>
<p>4. <u>No. 19950400123</u> F69, was placed on Prilosec therapy (ca. 20 mg/day) for the Tx of hiatal hernia. She experienced severe and intense hearing loss in her R ear.</p>	<p><u>Positive dechallenge?</u> The patient believed that the hearing loss may have been related to OME. (Closed)</p>
<p>5. <u>No. 19950600042</u> This is the sister of the above-listed patient. While on Tx with OME, this patient experienced temporary loss of hearing in her R ear. OME Tx was D/C; the symptom abated.</p>	<p>More information is needed but this seems to be a case of <u>positive dechallenge</u>.</p>
<p>6. <u>No. 19950100060</u> M78, subject of a publication in Dr. J. Dermatol. 243-244 (1995). While on Tx with OME (40 mg daily) he experienced severe bullous cutaneous Rx.</p>	<p>More information is needed. In this patient, high plasma concentrations of OME might have been reached, due to his age, decompensating liver cirrhosis, and also concomitant Tx with allopurinol.</p>
<p>7. <u>No. 19950800100</u> F49, developed bilateral loss of hearing which was audiotically documented, while on therapy with OME (40 mg daily) for the Tx of GU and DU.</p>	<p>In this patient, concomitant Tx include lansoprazole. She seems to have been administered high doses of PPIs.</p>
<p>8. <u>No. 19951000296</u> M27 was treated with OME for the Tx of DU; he developed L labyrinthine hearing loss.</p>	<p>The reporter indicated that a relationship between oral OME Tx and the AE was "urgently suspected".</p>
<p>9. <u>No. 19960600040</u> M 41, who was placed on Tx with OME 20 mg AM. When PRILOSEC Tx was increased to 40 mg (plus concomitant antibiotic to treat H pylori), the patient experienced hearing loss and tinnitus.</p>	<p><u>Positive dechallenge.</u> These AEs abated after PRILOSEC® therapy was D/C.</p>
<p>10. <u>No. 19960900139</u> M57 was placed on therapy with OME (20 mg p.o. daily) for the Tx of hyperacidity symptoms. It is not known whether the patient was taking any medication concomitantly. Subsequent to the start of omeprazole therapy, the patient experienced progressive vertigo symptoms as well as nausea. After about 10 days, high tone tinnitus and progressive loss of hearing occurred in the L ear...</p>	<p>In this patient, there was an apparent <u>temporal relationship</u> between the start of the drug and the AE.</p>
<p>11. <u>No. 19970300102</u> M49 was placed on Tx with OME 20 mg daily for the treatment of GERD. Concomitant medications included Pravachol 10 mg daily for the treatment of elevated cholesterol; 6 months later the patient developed tinnitus and increased frequency hearing loss according to an ENT physician.</p>	<p>In this patient, tinnitus and high frequency hearing loss were considered to be "permanently or substantially disabling conditions".</p>



#### IV. RECOMMENDATIONS FOR REGULATORY ACTION

- 1) It is recommended to approve the sponsor submission of July 31, 1998 [NDA 19-810 (SLR 057)]. The proposed labeling revisions to the ADVERSE REACTIONS Section of the labeling are acceptable as proposed by the sponsor:
  1. *Body as a Whole*: Add the phrase "Allergic reactions, including rarely, anaphylaxis (see also *Skin* below)"
  2. *Skin*: Add the phrase "purpura and/or petichiae (some with rechallenge)"
- 2) It is also recommended to ask the sponsor to submit a supplemental application providing for labeling changes addressing drug-induced hearing deficits in apparent association with OME administration. This recommendation is based on the review of the 37 cases of reduced hearing or deafness, in addition to the single patient [19970800129/.1998030034] reported to experience partial deafness followed by reduction in hearing while being treated with the drug. Among the 11 cases listed in Section III of this review, there were instances of temporal relationship between the AE and the drug, at least four instances where the reporter's assessment indicated a probable/possible relationship to drug and – contrary to what the sponsor states – several instances of apparent positive dechallenge.

Recommendation No. 2. should be handled on a separate letter to the sponsor.

*February 2, 1999*

*/S/*

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:

NDA 19-810

HFD-180

HFD-180/LTalarico

HFD-180/HGallo-Torres

HFD-181/PM

HFD-180/JChoudary

HFD-180/EDuffy

r/d 1/29/99

f/t 2/2/99 jgw

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**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 019810/S057**

**ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS**

JK

Division of Gastrointestinal & Coagulation Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 19-810/S-053, S-055, S-057

Name of Drug: Prilosec (omeprazole) Delayed-Release Capsules

DEC - 9 1998

Sponsor: Astra Pharmaceuticals, L.P.

Material Reviewed

Submission Date(s): October 19, 1998

Receipt Date(s): October 20, 1998

**Background and Summary Description:** The sponsor submitted a newly printed package insert (no. 7910930) which corrects errors discovered in the final printed labeling (FPL) for supplement 055 (new indication for the concomitant use of Prilosec, clarithromycin, and amoxicillin for *H. pylori* eradication; approved June 30, 1998) and adds a 1000 count bottle for the 10 mg capsules (approved August 17, 1998 in supplement 053). The new labeling also replaces the FPL submitted on July 31, 1998 in a "Special Supplement - Changes Being Effected" (supplement 057; action pending).

Review

The submitted FPL, identified as "7910930" was compared to the currently approved FPL, identified as "7010928" (approved June 30, 1998 in supplement 055). No differences were noted except for the following revisions identified in the marked-up version in this submission.

1. Under **CLINICAL PHARMACOLOGY**, *Clinical Studies, H. pylori Eradication in Patients with Duodenal Ulcer Disease, Triple Therapy*:

The word \_\_\_\_\_ was replaced by "Prilosec" in first sentence of the first paragraph as follows:

"Three U.S. randomized, double-blind clinical studies in patients with *H. pylori* infection and duodenal ulcer disease (n=558) compared **PRIOSEC** plus clarithromycin plus amoxicillin to clarithromycin plus amoxicillin."

2. Under **CLINICAL PHARMACOLOGY**, *Clinical Studies, H. pylori Eradication in Patients with Duodenal Ulcer Disease, Dual Therapy*:

The word \_\_\_\_\_ was replaced by "Prilosec" in the first and fourth sentences of the

first paragraph as follows:

"Four randomized, double-blind, multi-center studies (M93-067, M93-100, M92-812b, and M93-958) evaluated PRILOSEC 40 mg q.d. plus clarithromycin 500 mg t.i.d. for 14 days, followed by PRILOSEC 20 mg q.d. (M93-067, M93-100, M93-058) or PRILOSEC 40 mg q.d. (M92-812b) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*."

"These studies compared the combination regimen to PRILOSEC and clarithromycin monotherapies."

3. Under **CLINICAL PHARMACOLOGY, *Helicobacter, Helicobacter pylori, Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes:***

In the table under this section, the word "not" was removed from the phrase "*H. pylori* negative - not eradicated."

4. Under **CLINICAL PHARMACOLOGY, *Helicobacter, Helicobacter pylori, Amoxicillin Susceptibility test Results and Clinical/Bacteriological Outcomes:***

The phrase "in the omeprazole/clarithromycin/amoxicillin treatment group" was added to the first sentence as follows:

"In triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole/clarithromycin/amoxicillin treatment group who had pretreatment amoxicillin susceptible MICs ( $\leq 0.25$   $\mu\text{g/mL}$ ) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy."

Revisions 1-4 conform to the draft labeling approved on June 30, 1998 in Supplement 055 and are acceptable.

5. Under **HOW SUPPLIED:**

"NDC 61113-606-82 bottles of 1000" was added to the list of packages.

This revision was approved on August 17, 1998 in supplement 053 and is acceptable.

### Conclusions

The revisions are acceptable and the submitted FPL should be acknowledged and retained.

/S/

Maria R. Walsh, M.S.

Regulatory Project Manager

/S/

12-9-98

D

NDA 19-810/S-053, S-055, S-057

Astra Pharmaceuticals, L.P.  
Attention: Gary P. Horowitz, Ph.D.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677

DEC 10 1998

Dear Dr. Horowitz:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

We acknowledge the receipt of your October 19, 1998 submission containing a newly printed package insert (no. 7910930) which corrects errors discovered in the final printed labeling (FPL) for supplement 055 (new indication for the concomitant use of Prilosec, clarithromycin, and amoxicillin for *H. pylori* eradication; approved June 30, 1998) and adds a 1000 count bottle for the 10 mg capsules (approved August 17, 1998 in supplement 053). The new labeling also replaces the FPL submitted on July 31, 1998 in a "Special Supplement - Changes Being Effected" (supplement 057; action pending).

We have reviewed the labeling that you submitted and we find it acceptable.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,



12-9-98

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
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NDA SUPPL AGEMENT

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SE8/FA  
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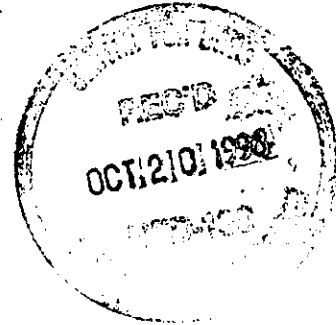
**ASTRA**<sup>®</sup>  
Astra Pharmaceuticals

Gary P. Horowitz, Ph.D.  
Regulatory, Liaison Director

10/27/98  
T

October 19, 1998

SLR/FA AF  
057



Lilia Talarico, M.D. - Director  
Division of Gastrointestinal and  
Coagulation Drug Products  
HFD-180, Room 6B-45  
Office of Drug Evaluation III (CDER)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Talarico:

**NDA 19-810/S-053; S-055; S-057: PRILOSEC<sup>®</sup> Delayed-Release Capsules  
(Omeprazole)  
GENERAL CORRESPONDENCE**

Please refer to the supplemental NDAs S-055 (new indication for concomitant use of PRILOSEC<sup>®</sup>, clarithromycin and amoxicillin for *H. pylori* eradication) and S-057 (addition of new information to labeling under ADVERSE REACTIONS), for which Final Printed Labeling was submitted on July 31, 1998. Please also refer to S-053 which provides for the packaging of the PRILOSEC<sup>®</sup> 10 mg capsules in a 1000 count bulk package.

The package insert submitted as FPL for S-055 and S-057 is identified by the component no. 7910928. The package insert was printed for S-053 (no. 7910929) but was not required for approval of the supplement.

With this letter we wish to inform you that subsequent to the submission of FPL for supplements S-055 and S-057, and the printing of the package insert for S-053, we discovered errors in these printed package inserts. Attached to this letter (Attachment 1) we are providing a newly printed package insert (no. 7910930) for your information that makes corrections to these errors. Attachments 2 and 3 provide marked up copies of the original FPL (package insert no. 7910928), and the package insert for S-053 (no. 7910929) detailing the errors and the corrections.

ORIGINAL

MAILING ADDRESS:

Astra Pharmaceuticals, L.P.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5677



We plan to implement the corrected package insert no. 7910930, which combines information from S-053, S-055 and S-057, in packaging of PRILOSEC® Delayed-Release Capsules in November, 1998, for distribution from the Merck Manufacturing facility in West Point, PA on or about December 1, 1998.

Please direct any questions or requests for additional information to me at (610) 695-1008 or, in my absence, to Barbara J. Blandin, Regulatory Project Manager at (610) 695-1540.

Sincerely yours,

Gary P. Horowitz, Ph.D.  
Director - Regulatory Liaison

Federal Express No:



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Attachment 3	Marked-up Version of Package Insert [No. 7910929; originally printed for S-053] for PRILOSEC® Delayed-Release Capsules Showing Changes Resulting in Package Insert No. 7910930	25

**APPEARS THIS WAY  
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**DRAFT LABELING**